This may be explained by the following factors:

- Narasin and nicarbazin act at different stages
- Narasin and nicarbazin affect different energy systems in the cell
- Narasin and nicarbazin impact both physical and biochemical components of the cell
- Narasin and nicarbazin require different genetic mutations for resistance development

Organisms progressing beyond the effects of the ionophore are subjected to the effects of nicarbazin. Then, the host's immune response can provide insurance against the very few organisms that may survive.

Response in broilers

The objective for controlling coccidiosis in broilers is to walk the fine line between too much and too little control. Anticoccidials used at excessive levels have a negative impact on broiler performance and are uneconomical.[15] However, commercial broiler houses are infected with ubiquitous coccidial populations, so the alternative practice of not using anticoccidials is not only detrimental to the birds' well-being but also results in poor performance and economic returns.[8,15] Maxiban's formula delivers a synergistic approach to coccidia control. Using the combination, allowing for optimal disease control, reduces the birds' level of drug exposure to both the ionophore and the chemical. This prudent use of anticoccidials minimizes dose-dependent negative effects.

Summary

Maxiban is a combination of narasin and nicarbazin. Each molecule affects a different energy pathway and is active during different stages of the parasite's life cycle. This combination presents substantial obstacles to resistance development and optimizes the effect of each molecule, allowing for reduced levels.

Key points

- Maxiban is a potentiated chemical — a combination of narasin and nicarbazin
- Maxiban kills coccidia by depleting the parasite's energy through two different paths
- The synergistic effect increases coccidial control while reducing potential resistance
- The synergistic effects of these dual modes of action also allow less drug exposure

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Coban directions for use:

- Feed Coban at
  – **90-110 g/ton**
- Feed continuously as the sole ration
- Requires a zero-day withdrawal (when fed according to the label)

CAUTION: Ingestion of monensin by horses and guinea fowl has been fatal.

Maxiban directions for use:

- Feed Maxiban at
  – **54-90 g/ton**
- Feed continuously as the sole ration
- Requires a 5-day withdrawal

CAUTION: Ingestion of narasin by adult turkeys, horses or other equine species has been fatal. Do not feed to laying hens.

Monteban directions for use:

- Feed Monteban at
  – **54-72 g/ton**
- Feed continuously as the sole ration
- Requires a zero-day withdrawal (when fed according to the label)

CAUTION: Ingestion of narasin by adult turkeys, horses or other equine species has been fatal. Do not feed to laying hens.

The labels contain complete use information, including cautions and warnings. Always read, understand and follow the labels and use directions.

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Poultry Science Update

Maxiban®'s Mode of Action and Impact on Coccidiosis Control

By Robert Evans, PhD, DVM, ACPV, Elanco Animal Health

Introduction

Maxiban® is an anticoccidial premix containing 36 grams of narasin and 36 grams of nicarbazin per pound. This approved product is an ionophore and chemical combination. This combination maximizes the benefits of each component and may minimize their potential negatives.[1,2] Research trials have documented Maxiban's effect on coccidia is greater than that achieved by either compound alone and exceeds the expected additive benefits for controlling coccidia.[1,2,3] This synergistic relationship between the product's two active ingredients classifies Maxiban as a potentiated chemical.

Mode of action on a molecular basis

The ionophore (narasin) and chemical (nicarbazin) that make up Maxiban each impact the coccidial cell's energy through different routes. Ultimately, it is this disruption of the cell's energy supply that leads to the control and death of the parasite. At a cellular level, coccidia primarily rely on two energy cycles known as glycolysis and the electron transport system. Glycolysis dominates the extracellular stages of the coccidial life cycle while in the bird's intestinal lumen. The electron transport system (ETS) dominates the parasite's stages after invading the cells of the intestinal wall. Glycolysis, acting in the absence of oxygen, generates two energy units from each molecule of glucose providing maintenance energy for the parasite. The ETS provides 15 times more energy units per glucose molecule that are used for growth and reproduction, but operates only when molecular oxygen is present.

As the coccidia progress through the bird's digestive tract, narasin acts on the coccidial cell membranes,[4] causing an influx of sodium (Figure 1). This reaction draws water into the parasite cells.[5,6] The coccidial organisms must deplete their maintenance energy reserves by utilizing their sodium-potassium pumps to remove the excessive sodium from the interior of their cells.[6] When the energy is depleted, the pumps no longer function. Coccidial cell lysis occurs when the resulting osmotic pressure inside the parasite becomes too great for its cell wall to withstand (Figure 2). Any organisms surviving exposure to narasin penetrate and enter the cell lining of the bird's intestine. They are also in a substantially weakened condition and are less efficient at reproduction.[4,7]

When a coccidial sporozoite enters a host enterocyte, it has ready access to molecular oxygen, and the ETS—located in the parasite mitochondria—is activated. The nicarbazin component of Maxiban short-circuits the oxidative-phosphorylation (O-P) process, which is critical to the parasite's ETS pathway[3]. This serves to deprive the invading

coccidia of their energy source required to maintain a stable environment, thus leading to the parasite's death.

Resisting resistance

The American Veterinary Medical Association says resistance occurs when a micro-organism develops the ability to survive and reproduce in the presence of an antimicrobial that used to prevent these actions. True resistance rarely occurs with ionophores.[3]

The term resistance is often inappropriately applied to organisms demonstrating reduced sensitivity to a particular anticoccidial.[9] This creates confusion when discussing program effectiveness and should be discouraged.

The rigidity of the cell wall is the most probable mechanism whereby the parasite develops reduced sensitivity to ionophores.[9] Physiological changes to the highly complex cell membrane require multiple genetic mutations.[9] Therefore, mutations are less likely to occur in the correct combinations.

As the cell wall becomes more rigid, it requires a greater concentration of the ionophore to facilitate the movement of sodium into the cell. More rigid membranes, however, present the dilemma that the parasite does not replicate as efficiently as those with more normal (less rigid) membranes. This is a major disadvantage for the resistant parasite and when an ionophore is not present or is present in reduced amounts, the coccidia strains with less rigid membranes quickly predominate. In addition, because ionophores do not stop 100 percent of the parasites from developing, the host's immune system is stimulated and provides additional control. The immune system does not recognize a difference in the sensitivity levels and will respond to any of the parasites.[9,10] This two-pronged approach to coccidiosis control, coupled with multiple genetic mutations necessary for resistance development, accounts for much of the long-term success of the ionophores.

Nicarbazin resistance requires development of a substitute biochemical pathway to bypass the O-P step of the ETS. Some scientists believe this requires a single genetic mutation when alternative electron acceptors are available. Indications are that judicious, commercial use of nicarbazin for many years has led to minimal nicarbazin resistance.[3] Imprudent use of nicarbazin for extended periods in a given environment could theoretically lead to populations with significant resistance to the chemical.[11] Studies have shown that when exposure to nicarbazin is ended, the coccidial population typically reverts to predominantly nicarbazin-sensitive strains.[5] This suggests inefficiencies of the alternative pathway are a disadvantage to the parasite and these organisms do not compete well with the sensitive population.

Nicarbazin's activity is most prominent during the intracellular stages of the coccidia life cycle. This is coincidental with the activation of the bird's immune system caused by the parasite entering the host cell. As with the ionophores, the bird's immune response can assist in controlling the disease.

The combined activity of narasin and nicarbazin places the parasite at a severe disadvantage. Those sporozoites not inactivated by the ionophore enter the host cell in a state of significant energy depletion and diminished reproductive capabilities. Nicarbazin blocks the ETS immediately after being absorbed into the parasite, causing the organism to either die or develop an alternative system.

The reduced level of anticoccidial exposure in this combination product may contribute to the slow development of resistant coccidial populations. Research data suggest resistance occurs through the selection of mutant strains and not through drug adaptation.[9,10,12,13,14] Additional studies indicate resistance to the combination ionophore and nicarbazin was maximized when drug levels were at higher, less economical levels.[11]

Figure 1
The coccidial life cycle and timing of activity of approved anticoccidials

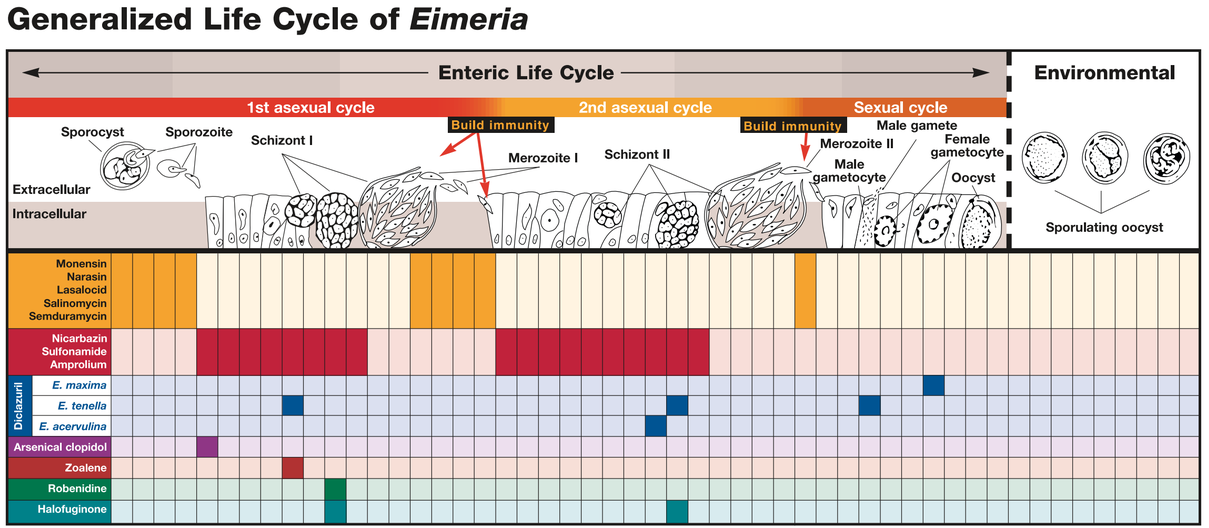
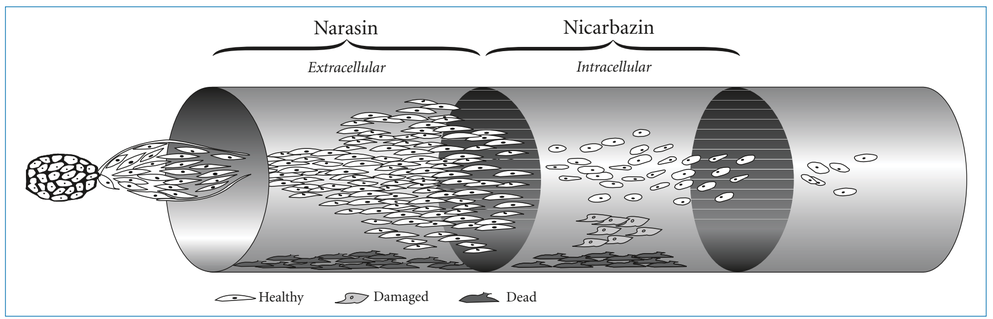


Figure 2
The effect of Maxiban on coccidial populations



Impact of Maxiban on coccidial populations

The coccidial population within the intestine of Maxiban-treated birds affected by the narasin component can be divided into three groups (Figure 2). The first are those parasites narasin will kill by disrupting osmotic balance, resulting in cell lysis. The second group consists of parasites narasin "damages," resulting in depleted cellular energy reserves. This group, while still alive, continues through its life cycle in a severely compromised state. The third group consists of parasites escaping the effect of the ionophore and progressing toward maturity.

There are several phases in the coccidia life cycle requiring the parasite to invade the cells of the bird's intestinal wall where nicarbazin is active. Nicarbazin quickly kills the energy-depleted parasites and the majority of all surviving coccidial organisms. Immunity is elicited as these organisms cycle through the cellular phases, but the majority are prevented from completion of their life cycle due to the effect of nicarbazin. Maxiban is recommended for use in the starter/grower to 28 days or beyond. Other ionophores, such as Coban® or Monteban®, are often used following Maxiban. Maxiban can be incorporated into well-designed anticoccidial programs to maintain product/program efficacy while maximizing performance.

Potentiation or synergy (1+1 = 3)

The development of an immune response reduces resistance development and complements the activity of the anticoccidials. However, this does not account for the complete benefit of the drug combination. Immunity is active when either of these molecules is used alone, but the actual combined impact is greater than what could be expected to occur.[2,3,15]